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[REDACTED] EXAMINER

LUKTON, DAVID

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23

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. <b>09/518,098</b>	Applicant(s) <b>Shapiro</b>
	Examiner <b>David Lukton</b>	Art Unit <b>1653</b>
		
<i>-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --</i>		
<b>Period for Reply</b> A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.		
<ul style="list-style-type: none"> <li>- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.</li> <li>- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.</li> <li>- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.</li> <li>- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).</li> <li>- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).</li> </ul>		
<b>Status</b> <p>1) <input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>Oct 30, 2002</u></p> <p>2a) <input type="checkbox"/> This action is FINAL.      2b) <input checked="" type="checkbox"/> This action is non-final.</p> <p>3) <input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i>, 1935 C.D. 11; 453 O.G. 213.</p>		
<b>Disposition of Claims</b> <p>4) <input checked="" type="checkbox"/> Claim(s) <u>1-52</u> is/are pending in the application.</p> <p>4a) Of the above, claim(s) <u>1-39, 41-45, 48, and 50-52</u> is/are withdrawn from consideration.</p> <p>5) <input type="checkbox"/> Claim(s) _____ is/are allowed.</p> <p>6) <input checked="" type="checkbox"/> Claim(s) <u>40, 46, 47, and 49</u> is/are rejected.</p> <p>7) <input type="checkbox"/> Claim(s) _____ is/are objected to.</p> <p>8) <input type="checkbox"/> Claims _____ are subject to restriction and/or election requirement.</p>		
<b>Application Papers</b> <p>9) <input type="checkbox"/> The specification is objected to by the Examiner.</p> <p>10) <input type="checkbox"/> The drawing(s) filed on _____ is/are a) <input type="checkbox"/> accepted or b) <input type="checkbox"/> objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).</p> <p>11) <input type="checkbox"/> The proposed drawing correction filed on _____ is: a) <input type="checkbox"/> approved b) <input type="checkbox"/> disapproved by the Examiner. If approved, corrected drawings are required in reply to this Office action.</p> <p>12) <input type="checkbox"/> The oath or declaration is objected to by the Examiner.</p>		
<b>Priority under 35 U.S.C. §§ 119 and 120</b> <p>13) <input type="checkbox"/> Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).</p> <p>a) <input type="checkbox"/> All b) <input type="checkbox"/> Some* c) <input type="checkbox"/> None of:</p> <ol style="list-style-type: none"> <li>1. <input type="checkbox"/> Certified copies of the priority documents have been received.</li> <li>2. <input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____.</li> <li>3. <input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).</li> </ol> <p>*See the attached detailed Office action for a list of the certified copies not received.</p> <p>14) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e). a) <input type="checkbox"/> The translation of the foreign language provisional application has been received.</p> <p>15) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.</p>		
<b>Attachment(s)</b> <p>1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)</p> <p>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)</p> <p>3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____</p> <p>4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____</p> <p>5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)</p> <p>6) <input type="checkbox"/> Other: _____</p>		

Pursuant to the directives of paper No. 22 (filed 10/30/02), claims 40, 42, 46 have been amended, and claims 47-52 added. Claims 1-52 are pending. Claims 1-39, 43-45 remain withdrawn from consideration; in addition, claims 41-42 are withdrawn because it does not encompass retrovir. In addition, claim 48 is withdrawn since the molecular weight of the elected species exceeds 20,000 D. Claims 50-51 are also withdrawn, since it appears that none of the recited sequences occurs within  $\alpha_1$ -antitrypsin. Also, claim 52 is withdrawn. It may be the case that  $\alpha_1$ -antitrypsin "comprises" the sequence FVFLM, but applicants' species election (paper No. 13, filed 8/6/01) for the "second compound" of claim 40 was retrovir. As it happens, retrovir does not encompass either of the sequences of claim 52. Accordingly, claims 40, 46, 47, 49 are examined in this Office action; claims 1-39, 41-45, 48, 50-52 are withdrawn from consideration.

Applicants arguments filed 10/30/02 have been considered and found persuasive in part. The previously imposed enablement rejection is withdrawn.

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Claims 40, 46, 47, 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was

filed, had possession of the claimed invention.

Claim 40 recites the following:

"the first compound is not serine leukocyte protease inhibitor".

A similar exclusion is present in claim 46.

It appears that the only location in the text (of the specification) that one could point to as justifying this exclusion would be the passage on page 6, line 16+, wherein the following is stated:

[The] **naturally occurring** ...inhibitor... **secretory** leukocyte protease inhibitor was shown to inhibit HIV in monocytic cells.

The first issue is that the phrase "serine leukocyte protease inhibitor" does not appear to be present anywhere in the specification. (Applicants are requested to point out the relevant page and line number). The second issue is that if there is indeed support for an exclusion, such an exclusion would be limited to the **naturally occurring secretory** leukocyte protease inhibitor. Thus, there is no support for inhibitors of secretory leukocyte protease inhibitor that are not naturally occurring; there is no support for deletion mutants of naturally occurring leukocyte protease inhibitor, there is no support for truncated forms of naturally occurring leukocyte protease inhibitor, and there is no support for compounds which are obtained by chemical modification of the naturally occurring leukocyte protease inhibitor. The claims would appear to exclude any compound that one could justifiably describe as a

serine leukocyte protease inhibitor, i.e., applicants appear to be trying to cast this inhibitor as a genus, rather than a species. However, there is no support for such a genus or implied genus. Accordingly, description for the claimed invention is lacking. It is suggested that the exclusion be limited to **naturally occurring secretory** leukocyte protease inhibitor.

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Claims 40, 46, 47, 49 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Each of claims 40 and 46 recite that a compound can exhibit an activity which is somehow "like" that of  $\alpha$ 1-antitrypsin. This renders the claims indefinite as to the manner in which and the extent to which, the compound must resemble  $\alpha$ 1-antitrypsin. Applicants have amended the claims to recite that the compound in question inhibits serine protease. However, this does not make the claim more clear; if anything, it adds a layer of uncertainty. What exactly is the difference between a compound that is (on the one hand) "like"  $\alpha$ 1-antitrypsin, and (on the other hand) a serine protease inhibitor? It would be helpful if applicants would provide a few examples of compounds that are included in one of these two categories but not the other. Or, if there is adequate descriptive support for it, applicants could simply delete all references to  $\alpha$ 1-antitrypsin, and simply recite that the first compound is an inhibitor of a serine protease.

\*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the

prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 40, 46, 47, 49 are rejected under 35 U.S.C. §103 as being unpatentable over Lezdey (USP 5,532,215) in view of Rideout (USP 4,818,538).

As indicated previously, Lezdey discloses (col 6, line 31) that serine protease inhibitors can inhibit HIV replication. The reference also discloses one or more serine protease inhibitors that are asserted to have this property. The reference also does not teach combining a serine protease inhibitor with an HIV protease inhibitor. Rideout discloses that retrovir inhibits HIV replication. Rideout does not teach combining retrovir with a serine protease inhibitor. It would have been obvious to one of ordinary skill to combine the two agents in order to achieve additive effects.

In response to this ground of rejection, applicants have argued that the following references disclose that  $\alpha_1$ -antitrypsin fails to inhibit HIV replication: Anderson (*J. Biol. Chem.* **268**, 24887, 1996) and Vollenweider F. (*Biochemical Journal* **314** ( Pt 2) 521-32, 1996).

It may be the case that under his assay conditions, Anderson was unable to obtain HIV replication inhibition with  $\alpha_1$ -antitrypsin. However, Anderson was able to inhibit HIV

replication with the  $\alpha_1$ -antitrypsin mutant designated  $\alpha_1$ -PDX. In addition, Anderson admitted (page 24890, col 2, last paragraph) that other investigators were able to inhibit furin using higher concentrations of  $\alpha_1$ -antitrypsin, and different assay conditions. If Anderson's analysis of the situation is correct, one might conclude that skilled medical practitioners might not embrace the use of  $\alpha_1$ -antitrypsin for treating HIV. But that is really not the issue. The question is whether one would have expected inhibition of HIV replication, not whether one would have expected an effective treatment for patients afflicted with HIV. Certainly Anderson suggests that at least one mutant of  $\alpha_1$ -antitrypsin will inhibit HIV replication, and Anderson does actually "leave the door open" for the possibility of some HIV inhibition occurring in the case of  $\alpha_1$ -antitrypsin, even if the degree of selectivity (over serine proteases other than furin) is minimal or non-existent. Furthermore, any suggestion that  $\alpha_1$ -antitrypsin is ineffective to inhibit HIV replication is neutralized by Shapiro, Leland (*FASEB Journal* 15(1), 115-122, 2001). In other words, whether a given scientist "stumbles onto the truth" fortuitously, or arrives at a discovery through careful, painstaking research makes little difference from the perspective of the validity of a teaching of a reference. The Shapiro disclosure vindicates the assertions of Lezdey; it makes little difference whether the assertions of Lezdey were the result of idle speculation or careful experimentation.

As for Vollenweider F. (*Biochemical Journal* 314 (Pt 2) 521-32, 1996), applicants have

argued that somewhere on page 530 or 531, there is a statement that  $\alpha$ 1-antitrypsin fails to inhibit HIV replication. However, it is not evident where this statement might be. It is noted, however, that the sentence bridging pages 529 and 530 makes reference to  $\alpha$ 1-antitrypsin. But the assay conditions are not specified, and so it cannot be determined whether the findings of Vollenweider contradict those of Lezdey.

Applicants have also argued that  $\alpha$ 1-antitrypsin does not enter the cell. Whether this is true or not, the claims make no such distinction between agents that enter cells, and those that do not.

The rejection is maintained.

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Claims 40, 46, 47, 49 are rejected under 35 U.S.C. §103 as being unpatentable over Eisenberg (U.S.P. 6,017,880) in view of Rideout (USP 4,818,538).

As indicated previously, Eisenberg discloses (col 2, line 7+; col 2, line 20+) that serine leukocyte protease inhibitor (SLPI) can inhibit HIV replication. The reference does not teach combining SLPI with an HIV protease inhibitor. Rideout discloses that retrovir inhibits HIV replication. Rideout does not teach combining retrovir with a serine protease inhibitor. It would have been obvious to one of ordinary skill to combine the two agents in order to achieve additive effects. It is true that the claims exclude "serine leukocyte protease inhibitor" (SLPI). However, the claims do not exclude the various analogs and

mutants of SLPI that are disclosed in the reference. For example, at col 4, line 44, the derivative "CLPI" is disclosed. Thus, the amendment to claim 40 is regarded as excluding one specie, but Eisenberg discloses a genus.

In response to the foregoing, applicants have pointed to Turpin J. A. (*Antiviral Research* 29 (2-3) 269-77, 1996) who has questioned the conclusions of others that SLPI inhibits HIV replication. Applicants are correct that Turpin has presented results of failed attempts to inhibit HIV replication. However, as stated on page 275, col 2, some antiviral activity was observed in the range of 1000 µg/mL. Turpin concludes that because of the high level of peptide required, the result is not of physiological relevance. Whatever the merits of Turpin's conclusion on this matter, the claims are not drawn to a method of achieving commercial success; nor are the claims drawn to a method of successfully treating HIV infections in humans by oral administration. Rather, the claims are drawn to a method of inhibiting HIV replication, without limits on the amount of protease inhibitor that is used. Accordingly, Turpin does not prove that there is no concentration at which SLPI is effective. In addition, even if it were true that evidence had been provided which discounted SLPI *per se*, this would not necessarily prove that the disclosed variants of SLPI are also ineffective.

Applicants have also pointed to McNeely (*Blood* 90, 1141, 1997). As it happens, this article undermines applicants assertion of "non-enablement" of "SLPI". It is stated in

the article that SLPI inhibits HIV infection of monocytes. The fact of this undermines applicants' arguments with respect to the Turpin reference. Applicants have also pointed to the finding of McNeely that some undefined C-terminal domain was not active. However, what the relationship of this C-terminal domain to anything that is disclosed in Eisenberg ('880) is not made clear by McNeely or by applicants. Thus, the McNeely reference reinforces the examiner's assertion that inhibition of HIV replication by SLPI is enabled. It is true, of course that SLPI *per se* has been excluded; however, none of the variants disclosed by Eisenberg ('880) has been excluded.

Accordingly, the rejection is maintained.

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Claims 40, 46, 47, 49 are rejected under 35 U.S.C. §103 as being unpatentable over Anderson (*J Biol Chem* 268 24887, 1993) in view of Rideout (USP 4,818,538).

Anderson discloses that a mutant  $\alpha_1$ -antitrypsin is effective to inhibit HIV replication. This mutant is designated  $\alpha_1$ -PDX, and contains the sequence -Arg<sup>355</sup>-Ile-Pro-Arg<sup>358</sup>- . Anderson does not suggest combinining  $\alpha_1$ -PDX with retrovir. Rideout discloses that retrovir inhibits HIV replication. Rideout does not teach combining retrovir with a serine protease inhibitor. It would have been obvious to one of ordinary skill to combine the two agents in order to achieve additive effects.

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Claims 40, 46, 47, 49 are rejected under 35 U.S.C. §103 as being unpatentable over Vollenweider F. (*Biochemical Journal* 314 (Pt 2) 521-32, 1996) in view of Rideout (USP 4,818,538).

Vollenweider discloses that the  $\alpha_1$ -antitrypsin mutant designated  $\alpha_1$ -PDX exhibits some degree of inhibition of HIV replication. Vollenweider does not suggest combining  $\alpha_1$ -PDX with retrovir. Rideout discloses that retrovir inhibits HIV replication. Rideout does not teach combining retrovir with a serine protease inhibitor. It would have been obvious to one of ordinary skill to combine the two agents in order to achieve additive effects.



Applicants are advised that, in each of claims 50 and 52, a colon, rather than a period should follow "NO", i.e., either of the following:

*SEQ ID NO:1* - or - *SEQUENCE ID NO:1*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



DAVID LUKTON  
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